

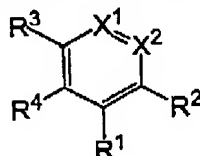
**PATENT APPLICATION**

Appln No. 10/826,982  
 Amdt. Dated July 26, 2006  
 Reply to Office Action of April 13, 2006

The listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims**

Claim 1. (currently amended). A compound of formula



or a pharmaceutically acceptable salt thereof, wherein

$X^1$  is  $C(R^4)$  or N

$X^2$  is  $C(R^2)$  or N; wherein at least one of  $X^1$  and  $X^2$  is N;

$R^1$  is  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  or  $-NR^aC_{2-6}alkylOR^a$  or  $C_{1-8}$ alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ ;

$R^2$  is  $C_{1-8}$ alkyl, phenyl, benzyl,  $R^c$ ,  $R^f$ ,  $C_{1-4}alkylR^c$ ,  $C_{1-4}alkylR^f$  or  $R^g$ ;

$R^3$  is phenyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ ;

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$R^4$  is phenyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-NR^a(C_{1-4}alkylR^f)$ ,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ ;

$R^a$  is independently at each instance H or  $R^b$ ;

$R^b$  is independently at each instance  $C_{1-8}$ alkyl, phenyl or benzyl;

$R^c$  is independently at each instance a saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the ring is fused with 0 or 1 benzo groups and 0 or 1 saturated or unsaturated 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 atoms selected from N, O and S; wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups;

$R^d$  is independently at each instance  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  or  $-NR^aC_{2-6}alkylOR^a$ ;

$R^e$  is independently at each instance  $C_{1-6}$ alkyl substituted by 1, 2 or 3 substituents independently selected from  $R^d$ ;

$R^f$  is independently at each instance  $R^c$  substituted by 1, 2 or 3 substituents independently selected from  $R^d$ ; and

$R^g$  is independently at each instance  $R^b$  substituted by 1, 2 or 3 substituents independently selected from  $R^c$ ,  $R^f$  and  $R^d$ .

2. (Original) A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier or diluent.

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**3. (Canceled)**

**4. (Original)** A method of treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic  $\beta$  cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound according to Claim 1.

**5. (Original)** A method of treatment of rheumatoid arthritis comprising administering an effective amount of a compound according to Claim 1.

**6. (Original)** A method of lowering plasma concentrations of either or both TNF- $\alpha$  and IL-1 comprising administering an effective amount of a compound according to Claim 1.

**7. (Original)** A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to Claim 1.

**8. (Original)** A method of treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to Claim 1.

**9. (Original)** The manufacture of a medicament comprising an effective amount of a compound according to Claim 1.

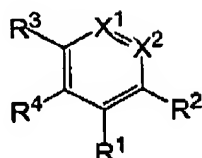
**10. (Canceled)****11. (Canceled)**

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12. (New) The compound of claim 1 wherein one of  $X^1$  and  $X^2$  is N and the other of one of  $X^1$  and  $X^2$  is C( $R^2$ ).

13. (New) A compound of formula



or a pharmaceutically acceptable salt thereof, wherein

$X^1$  is C( $R^2$ ) or N

$X^2$  is C( $R^2$ ) or N; wherein at least one of  $X^1$  and  $X^2$  is N;

$R^1$  is  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylINR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylINR^aR^a$  or  $-NR^aC_{2-6}alkylOR^a$  or  $C_{1-8}$ alkyl substituted by 1, 2 or 3 substituents independently selected from cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylINR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylINR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ ;

$R^2$  is  $C_{1-8}$ alkyl, phenyl, benzyl,  $R^c$ ,  $R^f$ ,  $C_{1-4}alkylR^c$ ,  $C_{1-4}alkylR^f$  or  $R^g$ ;

$R^3$  is phenyl, naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylINR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylINR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ ;

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$R^4$  is naphthyl, or a saturated or unsaturated 5- or 6-membered ring heterocycle containing 1-4 heteroatoms selected from N, O and S, wherein no more than 2 of the heteroatoms are O or S, and the heterocycle is substituted by 0, 1 or 2 oxo groups and is optionally fused with a benzo group, any of which are substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-6}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-NR^a(C_{1-4}alkylR^f)$ ,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ ;

$R^a$  is independently at each instance H or  $R^b$ ;

$R^b$  is independently at each instance  $C_{1-6}$ alkyl, phenyl or benzyl;

$R^c$  is independently at each instance a saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the ring is fused with 0 or 1 benzo groups and 0 or 1 saturated or unsaturated 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 atoms selected from N, O and S; wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups;

$R^d$  is independently at each instance  $C_{1-6}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  or  $-NR^aC_{2-6}alkylOR^a$ ;

$R^e$  is independently at each instance  $C_{1-6}$ alkyl substituted by 1, 2 or 3 substituents independently selected from  $R^d$ ;

$R^f$  is independently at each instance  $R^c$  substituted by 1, 2 or 3 substituents independently selected from  $R^d$ ; and

$R^g$  is independently at each instance  $R^b$  substituted by 1, 2 or 3 substituents independently selected from  $R^c$ ,  $R^f$  and  $R^d$ .

14. (New) The compound of claim 13 wherein one of  $X^1$  and  $X^2$  is N and the other of one of  $X^1$  and  $X^2$  is  $C(R^2)$ .

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15. (New) The compound of claim 13 wherein  $R^4$  is a pyridine or pyrimidine ring, optionally substituted by 0, 1, 2 or 3 substituents selected from  $C_{1-8}$ alkyl,  $C_{1-4}$ haloalkyl, halo, cyano, nitro,  $-NR^a(C_{1-4}alkylR^f)$ ,  $-C(=O)R^b$ ,  $-C(=O)OR^b$ ,  $-C(=O)NR^aR^a$ ,  $-C(=NR^a)NR^aR^a$ ,  $-OR^a$ ,  $-OC(=O)R^b$ ,  $-OC(=O)NR^aR^a$ ,  $-OC(=O)N(R^a)S(=O)_2R^b$ ,  $-OC_{2-6}alkylNR^aR^a$ ,  $-OC_{2-6}alkylOR^a$ ,  $-SR^a$ ,  $-S(=O)R^b$ ,  $-S(=O)_2R^b$ ,  $-S(=O)_2NR^aR^a$ ,  $-S(=O)_2N(R^a)C(=O)R^b$ ,  $-S(=O)_2N(R^a)C(=O)OR^b$ ,  $-S(=O)_2N(R^a)C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $-N(R^a)C(=O)R^b$ ,  $-N(R^a)C(=O)OR^b$ ,  $-N(R^a)C(=O)NR^aR^a$ ,  $-N(R^a)C(=NR^a)NR^aR^a$ ,  $-N(R^a)S(=O)_2R^b$ ,  $-N(R^a)S(=O)_2NR^aR^a$ ,  $-NR^aC_{2-6}alkylNR^aR^a$  and  $-NR^aC_{2-6}alkylOR^a$ .

16. (New) A pharmaceutical composition comprising a compound according to Claim 13 and a pharmaceutically acceptable carrier or diluent.

17. (New) A method of treatment of rheumatoid arthritis comprising administering an effective amount of a compound according to Claim 13.

18. (New) A method of lowering plasma concentrations of either or both TNF- $\alpha$  and IL-1 comprising administering an effective amount of a compound according to Claim 13.

19. (New) A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to Claim 13.

20. (New) A method of treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to Claim 13.

21. (New) The manufacture of a medicament comprising an effective amount of a compound according to Claim 13.